IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mehraban et al.	Examiner:	Yao, Lei
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Tech Center:	Biotechnology and Organic Chemistry (1600)		
Title:	DIFFERENTIALLY EXPRESSED GENES INVOLVED IN ANGIOGENESIS, THE POLYPEPTIDES ENCODED THEREBY, AND METHODS OF USING THE SAME		

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APPELLANT'S REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This Reply Brief is presented in response to the Examiner's Answer dated November 20, 2008. A Notice of Appeal was filed on May 20, 2008, and an Appeal Brief was filed on August 19, 2008. Applicants submit this Reply Brief is timely filed as January 20, 2009 was a Federal holiday within the District of Columbia and the Reply Brief is being submitted on the next succeeding business day, January 21. 2009. 37 C.F.R. §1.7.

An oral hearing is requested. A separate request for oral hearing with the appropriate fee is filed herewith.

I. STATUS OF CLAIMS

Claims 56 and 69-79 are pending. Claims 1-55, 57-68, and 80 are cancelled. No claims are allowed. No claims are objected to. Claims 56 and 69-79 are rejected. Claims 56 and 69-79 are being appealed.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 56 and 69-79 lack enablement and are, therefore, unpatentable under 35 U.S.C. § 112, first paragraph.

III. ARGUMENT

Appellants submit this Reply Brief in response to the Examiner's Answer dated November 20, 2008. All of the pending claims stand rejected as unpatentable over 35 U.S.C. § 112, first paragraph for lack of enablement. The arguments presented in the Appeal Brief are hereby incorporated by reference in their entirety.

The following arguments are applicable to independent claim 56 unless specifically addressed to a particular claim. As dependent claims 69-79 depend from claim 56, the following arguments are also applicable to all of the dependent claims unless specifically addressed to a particular claim.

Introduction

The discovery of agents that inhibit angiogenesis has been an exciting new development. A number of antibodies or other inhibitors of angiogenesis have been approved for the treatment of cancer and other diseases. Many of these inhibitors are currently in phase II and phase III clinical trials. Appellants have identified a secreted glycoprotein, stanniocalcin, which is associated with angiogenesis. Appellants have demonstrated that the expression of stanniocalcin is upregulated in an endothelial tube formation model, is upregulated in various tumor tissues, and that expression is detected in the tumor tissue of a number of different cancer types. Appellants' specification describes that an antibody to this protein can inhibit angiogenesis.

Appellants' claim 56 is directed to a method for inhibiting angiogenesis in a tumor by administering to a tumor an effective amount of an antibody or antigen binding fragment of the antibody that specifically binds a polypeptide comprising an amino acid sequence of SEQ ID NO:76 and inhibits or neutralizes said polypeptide. The specification provides a description of the polypeptide and several working examples.

The amino acid sequence of SEQ ID NO:76 corresponds to PA23, which is defined in the specification at Table 1 on page 11 and page 25, lines 10-14 as a stanniocalcin precursor with GenBank accession number U25997. In the non-final Office Action mailed on March 5, 2004, the Examiner required Appellants to amend the disclosure to include the amino acid sequence of PA23, which was incorporated by reference in the specification as originally filed. In the Amendment and Response filed on September 2, 2004, Appellants amended the claims, sequence listing, and disclosure to include the nucleotide (SEQ ID NO:75) and amino acid (SEQ

ID NO:76) sequence for stanniocalcin precursor. Appellants have also described how to make antibodies and how to identify antibodies that inhibit or neutralize stanniocalcin at pages 85 to 95 in the specification. Methods of making antibodies and screening antibodies for inhibition or neutralization are also known to those of skill in the art.

Appellants disclose a working example showing upregulation of stanniocalcin precursor in an art recognized model for angiogenesis, endothelial tube formation. *See* Example 19 in the specification at page 142 and Fig. 23. Stanniocalcin precursor expression was found to be dramatically enhanced under tube-forming conditions, demonstrating a strong correlation between expression of stanniocalcin and tube-formation. *See* the specification at page 25, lines 20-26 and Example 19 at page 142. Appellants also disclose that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature but not in normal vessels. *See* the specification at page 145, line 32 to page 146, line 7 and Figures 28 and 29. The combination of increased expression in endothelial cells in a model for angiogenesis, and increased expression in tumor tissue provides a reasonable correlation of the relationship of upregulation of stanniocalcin with angiogenesis in tumor tissues. This correlation indicates that antagonists of stanniocalcin would be useful for inhibiting tumor angiogenesis.

Appellants have also provided confirmatory evidence of the association of stanniocalcin with different tumor types, such as breast cancer and colon cancer. In addition, Appellants have provided confirmatory evidence of the association of stanniocalcin with angiogenesis. This confirmatory evidence also further supports the reasonable correlation of the upregulation of stanniocalcin with angiogenesis in tumor tissues.

The Examiner argues in the Office Action dated April 25, 2006, in the Final Office Action dated October 13, 2006, in the Office Action dated June 28, 2007, in the Final Office Action dated February 28, 2008, and the Examiner's Answer of November 20, 2008 that the specification does not provide any guidance or objective evidence that inhibiting or neutralizing stanniocalcin in a mammal or tumor would effectively inhibit angiogenesis. The Examiner further argues in the Office Action dated April 25, 2006, in the Final Office Action dated October 13, 2006, in the Office Action dated June 28, 2007, in the Final Office Action dated February 28, 2008 and the Examiners Answer of November 20, 2008 that objective evidence

such as a working example is necessary to enable one skilled in the art to make and/or use the claimed invention because treatment of cancer in general including with antibodies is unpredictable. Appellants respectfully do not agree.

There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. United States Patent & Trademark Office, Manual of Patent Examining Procedure § 2164.01(a) (hereinafter MPEP) (citing *In Re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Only a reasonable correlation between the specification and the scope of enablement is required. MPEP § 2164.02 (citing *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985)) (emphasis added). If all the other factors point toward enablement, the lack of working examples will not by itself render the claimed invention non-enabled. MPEP § 2164.02.

An enabling disclosure only requires a reasonable correlation to the scope of the claims. The Examiner's apparent position that the specification cannot teach how to use the claimed method unless it provides a working example that provides objective evidence that inhibiting stanniocalcin in a tumor would effectively inhibit angiogenesis is contrary to controlling case law. *See, e.g., In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). In *Brana*, the claims were directed to compounds disclosed as anti-cancer agents. *Id.* at 1562. The USPTO rejected the claims as nonenabled, *id.* at 1563-64, despite working examples in Brana's specification showing treatment of cancer in a mouse model. *Id.* at 1562-63. The *Brana* court held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Therefore, whether the treatment will prove to be effective in humans is not a reasonable standard by which to measure enablement.

"The enablement analysis must be focused on the product or method defined by the claims." *Ex parte Zhang*, Appeal 2008-2455 (Bd. Pat. App. & Int. 2008) at page 5

(http://des.uspto.gov/Foia/ReterivePdf?system=BPAI&flNm=fd20082455-09-29-2008-1)[1]. The Board in *Ex parte Zhang* went on to state:

> "It is true that the Specification contemplates the uses of the claimed method to treat heart failure and other cardiac disorders, but practicing the claimed method does not require a therapeutically effective result." *Ex parte Zhang* at page 6.

Similarly, Appellants' claims are directed to a method of inhibiting angiogenesis in a tumor, but practicing the claimed method does not require a therapeutically effective result. Although Appellants' specification contemplates treating tumors and cancer, the claim is directed to a method of inhibiting angiogenesis. Clinical efficacy is not the standard by which to assess enablement of the claimed method. As the Board stated in *Ex parte Zhang*:

> "However, enablement especially in the context of pharmaceutical inventions-includes an expectation of further research and development. In the pharmaceutical field, an invention can be enabled well before it is ready to be administered to humans. Thus, enablement is not precluded even if the claims encompass methods, such as gene therapy, that have not yet overcome all obstacles to their clinical use." *Ex parte Zhang* at page 7.

An example is not necessary if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without an undue amount of experimentation MPEP § 2164.02. A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737 (emphasis added); *see also In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). The mere fact that that the experimentation may be difficult and time consuming does not mandate a conclusion that such experimentation would be considered undue, as great expenditures of time and effort may ordinarily be employed in the field. *Falko-Gunter vs. Inglis,* 448 F.3d 1357, 1367 (Fed. Cir. 2006).

Moreover, a claim does not lack enablement merely because it encompasses inoperative embodiments. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed.

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[1] *Ex parte Zhang* was decided September 29, 2008, which is after the filing date (August 19, 2008) of the Appeal Brief. Appellants have updated the Evidence Appendix in the current paper, specifically part D. CASES CITED IN THE BRIEF, to cite *Ex parte Zhang*.

Cir. 1984). Thus, claims to a method do not lack enablement merely because a difficult-to-achieve outcome is encompassed by the claims. *See In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims encompassing achieving full head of hair held enabled by evidence showing three-fold increase in hair number, filling-in, and fuzz).

The Examiner bears the initial burden of showing that a claimed invention is nonenabled. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971). "[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

Applying these standards, Appellants assert the claims are enabled by the specification and would not require undue experimentation. Appellants submit that the Examiner has not met her burden to show the claimed invention is non enabled. The standard for enablement being applied by the Examiner is much too stringent and not in accord with the case law. Even if it can be concluded that the Examiner has met the initial burden, Appellants have provided evidence that clearly establishes the enablement of the claimed subject matter and rebuts the position of the Examiner.

Argument

Claims 56 and 69-79

There are many factors to be considered in an analysis of enablement, including breadth of the claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quantity of experimentation. A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737 (emphasis added). A method of inhibiting angiogenesis as

described by the specification is enabled, interalia, through the use of the art recognized model of angiogenesis, and demonstration of expression of stanniocalcin in the vasculature of tumor tissue.

In the Examiner's Answer on pages 4-5, the Examiner contends that the specification does not provide critical guidance and objective evidence that inhibition of angiogenesis with the antibody as claimed would result in reduction in tumor growth or metastasis in a mammalian subject. Appellants submit that this is not the appropriate standard to evaluate enablement of a claim to a method of inhibiting angiogenesis and further, that the evidence in the specification provides enablement for the claimed methods.

As discussed above in reference to *Ex parte Zhang* and *In re Brana*, enablement focuses on the claimed subject matter. A showing of clinical efficacy is not required. The claimed subject matter at issue here is directed to a method of inhibiting angiogenesis in a tumor and does not require reducing tumor growth or metastasis as asserted by the Examiner. Appellants submit that the disclosure in the specification provides sufficient guidance to practice the invention as claimed.

The claims are directed to a method of using an antibody that specifically binds and inhibits or neutralizes a polypeptide comprising an amino acid sequence of SEQ ID NO:76. Appellants have described making and screening antibodies that specifically bind to the polypeptide. Appellants have provided evidence that the expression of stanniocalcin precursor correlates with an increase in angiogenesis. The specification provides a working example showing upregulation of stanniocalcin precursor in endothelial cells undergoing tube formation. *See* Example 19 in the specification at page 142 and Fig. 23. The endothelial cell model for tube formation is an art recognized model for angiogenesis. Davis *et al.*, *An α2β1 Integrin-Dependent Pinocytic Mechanism Involving Intracellular Vacuole Formation & Coalescence Regulates Capillary Lumen and Tube Formation in Three-Dimensional Collagen Matrix* 224 Experimental Cell Res.39, 39-51 (1996) (cited in IDS of September 2, 2004). The specification teaches that stanniocalcin precursor expression is dramatically enhanced under tube-forming conditions. *See* the specification at page 25, lines 20-26 and Example 19 at page 142. In contrast, lower levels of stanniocalcin precursor are expressed under conditions that do not foster tube formation. This data demonstrates a strong correlation between expression of stanniocalcin and tube-formation.

Appellants also examined tissue samples from tumor tissue and demonstrated expression of stanniocalcin precursor in the tumor vasculature but not in normal vasculature. The specification shows that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature, but is not expressed in normal vessels. *See* the specification at page 145, line 32 to page 146, line 7 and Figures 28 and 29. The combination of increased expression in endothelial cells in an art accepted model for angiogenesis, and increased expression in tumor tissue provides a reasonable correlation of the relationship of upregulation of stanniocalcin with angiogenesis in tumor tissues. Appellants therefore submit that they have provided working examples and sufficient guidance.

Ex parte Zhang and *In re Brana* also recognize that with regard to pharmaceutical inventions, there is an expectation of further experimentation and research, and that such experimentation is not undue even if clinical obstacles may be present. As discussed previously, use of agents to inhibit angiogenesis is known to those of skill in the art. Antibodies that inhibit angiogenesis *in vitro* have been shown to inhibit angiogenesis *in vivo*. For example, several anti-VEGF antibodies were known to inhibit angiogenesis both *in vitro* and *in vivo* and have been approved by the FDA for treating cancer. The success of anti-angiogenesis agents, including antibody antagonists, in treating cancer prompted the FDA commissioner to state that anti-angiogenesis therapy is the fourth modality of cancer treatment, the other three modalities being surgery, radiation, and chemotherapy. *See* Folkman, *Angiogenic Inhibitors: A Fourth Modality of Anticancer Therapy* 4 Community Oncology 296, 296-98 (2007) (cited in IDS of November 27, 2007). As of May 2007, nine angiogenic inhibitors were approved by the FDA and in more than 30 other countries to treat cancer. At least 50 other angiogenic inhibitors with varying degrees of anti-angiogenic activity are in phase II and phase III clinical trials. The examiner has not presented any evidence or reasoning to doubt the objective truth of the claims and specification that an antibody to stanniocalcin can inhibit angiogenesis.

Thus, Appellants submit that the Examiner has not established a *prima facie* case of lack of enablement of the claimed subject matter.

In the Examiner's Answer at page 9, the Examiner contends that Appellants have not provided *in vivo* evidence that the expression of stanniocalcin correlates with an increase in

angiogenesis. Appellants disagree. The specification provides evidence of in situ hybridization of tumor tissue showing expression of stanniocalcin in ductal mammary adenocarcinoma and squamous cell carcinoma. *See* the specification at Figures 28 and 29. The specification also states that no significant expression is seen in normal blood vessels. These results are characterized as *in vivo* because the specification indicates that they were obtained by whole mount hybridization of tumor tissue samples according to the method of Rosen *et al.*, Trends in Genetics 9:162-167 (1993) . *See* the specification at page 145, lines 2-5. Appellants further submit whether or not these results can be characterized as *in vivo* or *in vitro*, the specification indicates that the expression of stanniocalcin in tumor vasculature is enhanced as compared to expression in normal vasculature.

At page 10 of the Examiner's Answer, the Examiner further contends that it is not clear that that the expression of mRNA is the result of angiogenesis in the tumor or results in angiogenesis or plays a role in angiogenesis in tumor. Appellants disagree. As discussed previously, the standard for enablement requires a reasonable correlation between the scope of the claimed subject matter and the disclosure in the specification. Appellants contend that they have established this correlation by showing increased expression in an art recognized model for angiogenesis. The examiner admits that this is an art recognized model of angiogenesis in the Office Action of February 20, 2007 at page 7. The timing of the expression of stanniocalcin correlates with the formation of capillaries as described by Davis, cited supra. No increase in expression is seen in endothelial cells that do not undergo tube formation. Tumor tissues are known to be tissues that undergo angiogenesis and the enhanced expression of stanniocalcin in the tumor tissue as determined by in situ hybridization further supports the reasonable correlation between upregulation of expression of stanniocalcin and angiogenesis.

The Examiner also contends that it is not clear at what stage the stanniocalcin precursor could function as an angiogenesis factor. *See* page 11 of the Examiner's Answer. Appellants disagree. As discussed above, increased expression of stanniocalcin is seen in endothelial cells during tube formation. One of skill in the art reading the specification would understand that an antibody to stanniocalcin could effectively inhibit angiogenesis in tumor tissues undergoing angiogenesis. Moreover, the timing of administration could readily be determined by those of skill in the art using routine methods.

At page 15 of the Examiner's Answer, the Examiner states that "Neutralization of the activity of one protein does not guarantee to inhibit the entire or part of the angiogenesis process." Appellants submit that the Examiner is not using the proper standard for enablement as a guarantee is not required. In addition, the enablement standard does not require enablement of a perfected commercial embodiment. *See Ex parte Zhang* at page 5. The claimed method is directed to inhibiting angiogenesis and does not require that all angiogenesis in the tissue is inhibited.

Appellants submit that the level of skill in this art is high and the use of antibodies in inhibiting angiogenesis is not unpredictable. The Examiner's position concerning unpredictability of treatment of cancer does not take into account that a method of inhibiting angiogenesis as described by the specification is enabled, interalia, through the use of the art recognized model of angiogenesis.

Appellants submit the references cited by the Examiner do not accurately reflect the state of the art of use of antibodies for inhibiting angiogenesis. At least one of the cited references is almost 20 years old. Appellants have submitted evidence that the art of administering antibodies for inhibition of angiogenesis has advanced. Antibodies that inhibit angiogenesis *in vitro* have been shown to inhibit angiogenesis *in vivo*.

Appellants further contend that the Examiner is requiring Appellants to establish enablement to a higher degree of certainty than is required. The significant emphasis by the Examiner on the lack of clinical efficacy and alleged inability of the specification to guarantee success *in vivo*, in effect is requiring clinical data to establish enablement. In the Final Office Action of February 20, 2008 on page 5, the Examiner states:

> "Again as discussed in the rejection above: overview of monoclonal antibody therapy including some promising activity, however, major obstacles **for clinical efficacy** still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity.. . etc. Applicant has neither shown that claimed method have been experimented and successfully done, nor shown the evidence or direction indicating predictable expectation of success of claimed method, which could allow one skilled in the art to practice it without undue a quantity of experimentations."(emphasis added)

Appellants submit that the standard required for enablement is not one of clinical efficacy. As stated in *Brana*, the Federal Circuit indicated that "[t]he stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." 51 F.3d at 1568.

Appellants submit that an enabling disclosure only requires a reasonable correlation to the scope of the claims and a claim does not lack enablement merely because it encompasses inoperative embodiments. *Atlas Powder*, 750 F.2d at 1576. Again, the Examiner is using an improper standard to assess enablement of the claimed subject matter. In the Final Office Action of February 20, 2008 on page 6, the Examiner states:

> "However, it does not **guarantee** to neutralize the function of the stanniocalcin protein and used for inhibiting angiogenesis in a tumor in vivo because one skilled in the art clearly know a) antibody binding to its antigenic protein would not be necessary to neutralize the function of the protein and b) tumor angiogenesis is a complicated process in which many factors or proteins are involved, blocking a function of a protein **may not inhibit or affect the entirety of the angiogenic process** in a tumor, especially in vivo." (emphasis added)

Appellants submit the standard for enablement does not require a guarantee or that the method work to inhibit or affect the entirety of the angiogenic process. *See In re Cortright*, 165 F.3d at 1359 (claims encompassing achieving full head of hair held enabled by evidence showing three-fold increase in hair number, filling-in, and fuzz).

Moreover, Appellants submit that if any experimentation were required it would be routine experimentation. A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d at 737 (emphasis added). The mere fact that that the experimentation may be difficult and time consuming does not mandate a conclusion that such experimentation would be considered undue, as great expenditures of time and effort may ordinarily be employed in the field. *Falko-Gunter*, 448 F.3d at 1367.

Appellants submit that they have described methods and animal models for determining the efficacy of antibodies, for example, at page 76 of the specification, lines 1-25. Other *in vitro* and *in vivo* angiogenesis methods are known to those of skill in the art. Formulations and dosage for antibodies have been described, for example, at page 77 of the specification. Additional guidance for administration and dosage of antibody treatment is known to those of skill in the art

including as described in Presta *et al.*, *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors & Other Disorders* 57 Cancer Res. 4593, 4593-4599 (1997) (cited in IDS of September 2, 2004 and July 25, 2006). Appellants submit one of skill in the art reading the specification combined with knowledge of administration of other antibodies or anti angiogenesis treatments would be enabled to use the claimed subject matter without undue experimentation.

Thus, Appellants submit that the Examiner has not met her burden to show the claimed invention is nonenabled. The standard for enablement being applied by the Examiner is much too stringent and not in accord with the case law. The standard for enablement does not require clinical efficacy or a guarantee. All that is required is a reasonable correlation between the specification and the claims. Appellants submit one of skill in the art reading the specification would find a reasonable correlation between angiogenesis and increased expression of stanniocalcin. Appellants further submit that if any experimentation is required such experimentation is routine and the specification provides guidance as to how the experimentation should proceed. Appellants request that the Board reverse the rejection of the claims on this basis.

Even if, in the unlikely event, that the Examiner is found to have met the initial burden for establishing that the claims are nonenabled, Appellants submit they have provided evidence that confirms the enablement of Appellants' claims and rebuts the position of the Examiner.

Several post filing date references confirm the correlation of expression of stanniocalcin and angiogenesis described in Appellants' specification. For example, Filvaroff *et al.* found that transgenic mice over expressing stanniocalcin had significantly higher capillary density in organs and muscles compared with age-matched wildtype littermates. *See* Filvaroff *et al.*, *Stanniocalcin 1 Alters Muscle & Bone Structure & Function in Transgenic Mice* 143 *Endocrinology* 3681, 3689, first column, third paragraph (2002) (cited in IDS of September 2, 2004 and February 1, 2006). Filvaroff *et al.* also found that stanniocalcin 1 transgenic mice showed a larger increase in vascularity after femoral ligation compared to wildtype littermates. Thus, overexpression of stanniocalcin 1 leads to an increase in vascularity *in vivo*. This data further supports involvement of stanniocalcin in angiogenesis.

The examiner contends that the Filvaroff reference teaches away from the claimed invention. Appellants disagree and contend the Examiner is not reading the reference as a whole. When the reference is read as a whole, the Filvaroff reference shows that when angiogenesis was activated in the mice after femoral ligation, the transgenic mice expressing stanniocalcin had a larger increase in vascularity than wild type littermates subjected to the same procedure. This results of this reference confirm the findings as described by Appellants that an increase in stanniocalcin correlates with an increase in angiogenesis.

Gerritsen *et al.* studied gene expression using three different *in vitro* angiogenic models:HGF and VEGF in collagen gel; PMA, VEGF, and BFGF in collagen gel; and PMA, VEGF, bFGF in fibrin gel. *See* Gerritsen *et al.*, *In Silico Data Filtering to Identify New Angiogenesis Targets From a Large* In Vitro *Profiling Data Set* 10 Physiological Genomics 13 (2002) (cited in IDS of November 27, 2007 and May 24, 2005). Stably induced genes from each of these three models were identified and compared. Stanniocalcin was identified as one of the genes whose expression was upregulated in all three models and was stably upregulated through tube formation (48 hours). *See id.* at Figure 3A. Stanniocalcin was further evaluated for its role in angiogenesis in VEGF corneal tissue and expression in VEGF treated eyes was found to be dramatically higher. *Id.* (emphasis added).

Zlot *et al.* confirm that PMA stimulates the release of stanniocalcin from endothelial cells. *See, e.g.*, Zlot *et al.*, *Stanniocalcin 1 is an Autocrine Modulator of Endothelial Angiogenic Responses to Hepatocyte Growth Factor* 278 Journal of Biological Chemistry 47654, 47655, Table 1 (2003) (cited in IDS of September 2, 2004 and February 1, 2006). The gels in the angiogenesis tube formation assay shown in the specification were supplemented with PMA and Appellants show expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation. *See*, for example, the specification at page 123, line 17.

Kahn *et al.* demonstrated that stanniocalcin is upregulated in an endothelial cell tube model from the start of initial tube formation through full formation of the tubes (48 hours) as measured using the gene calling method and reverse transcriptase polymerase chain reaction. *See* Kahn *et al.*, *Gene Expression Profiling in an* In Vitro *Model of Angiogenesis* 156 The Am. J. of Pathology 1887 (2000) (cited in IDS of September 2, 2004 and February 1, 2006). Significantly, when tube formation was inhibited using a PPAR ligand, 15d-PGJ2, the expression

level of stanniocalcin was decreased. *See id.* at Table 4. The correlation of a decrease in expression with inhibition of tube formation in Kahn *et al.* is evidence in support of the contention that inhibition of angiogenesis is correlated with inhibition of stanniocalcin.

Several post filing date articles confirm an association of the upregulation of expression of stanniocalcin with tumor tissue undergoing angiogenesis. Gerritsen *et al.* compared gene expression in colon tumor samples versus normal tissue, and stanniocalcin was found to be one of the most highly upregulated genes in colon tissue. *See* Gerritsen *et al.* at Figure 3B. Stanniocalcin expression was also shown in colon adenocarcinomas by *in situ* hybridization. *See id.* at Figure 5. McCudden *et al.* demonstrated that STC-1 and its receptor co-localized in breast cancer cells in 91% of cases. *See* McCudden *et al., Co-localization of Stanniocalcin-1 Ligand & Receptor in Human Breast Carcinomas* 213 Molecular Cellular Endocrinology 167 (2004) (cited in IDS of February 1, 2006 and April 11, 2007). Yeung *et al.* demonstrated stanniocalcin was induced in human tumor cells, such as colon carcinoma, nasopharyngeal cancer, and ovarian cancer cultured under hypoxic conditions. *See* Yeung *et al., Hypoxia-Inducible Factor-1 in Human Activation of Stanniocalcin-1 in Human Cancer Cells* 146 Endocrinology 4951 (2005) (cited in IDS of November 27, 2007).

Wascher *et al.* demonstrated STC-1 was localized in invasive and ductal carcinoma in situ using an antibody to STC-1. STC-1 mRNA was detected in breast cancer cells by *in situ* hybridization and correlated with primary tumor size, number of positive lymph nodes, and stage of the cancer cell. *See* Wascher *et al., Stanniocalcin-1: A Novel Molecular Blood & Bone Marrow Marker for Human Breast Cancer* 9 Clinical Cancer Res. 1427 (2003) (cited in IDS of April 11, 2007).

The Examiner contends that these references show nothing more than stanniocalcin is detected in some tumor tissues. The Examiner points out that no antibody treatment has been disclosed in these references. See the Examiners Answer at page 19. Appellants submit that these references confirm the correlation between upregulation of stanniocalcin expression and secretion in many different types of tissues undergoing angiogenesis as described in the specification. The fact that others have not used an antibody as a treatment is not relevant to analysis of the enablement of the specification. The use of an antibody to stanniocalcin to inhibit angiogenesis is the subject of Appellants claimed invention.

At page 19 of the Examiner's Answer, the Examiner points to the Gerritsen reference in order to assert that STC protein does not have a role in endothelial cell proliferation and tube formation in angiogenesis. The passage from Gerritsen cited by the Examiner at page 19 of the Examiner's Answer refers to the Zlot reference. In the Zlot reference, STC protein appears to inhibit the morphogenesis activity of HGF in an *in vitro* matrigel assay. However, the Zlot reference also shows an increase in STC during active angiogenesis in the *in vivo* femoral ligation model even when HGF expression is also elevated. See Figure 6, page 47658. Thus, Appellants submit when the Zlot reference is read as a whole it does not support the Examiner's position that STC protein does not have a role in angiogenesis.

The Examiner at page 20 of the Examiner's Answer, again, is holding Appellants to a higher standard for enablement than established by the case law. In reference to anti-VEGF antibodies, the Examiner contends that clinical evidence has been submitted to the FDA to establish the treatment of tumors with anti-VEGF antibodies. As discussed previously, clinical efficacy is not the standard for enablement. Moreover, Appellants have provided these references in order to show that inhibiting angiogenesis with an antibody is not unpredictable and in order to refute the Examiner's citation of Mook et al.

Finally, the Examiner states that the *in vitro* model cannot predict inhibition of angiogenesis. Appellants disagree. The standard for enablement is whether one of skill in the art would be able to practice the claimed invention without undue experimentation. A reasonable correlation is all that is required and that such a correlation can be established by *in vitro* evidence. If the art is such that a particular model is recognized as correlating to a specific condition, then the model should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 51 F.3d at 1566; MPEP § 2164.02. Moreover, Appellants submit that the specification discloses more than just the *in vitro* model, it also describes the enhanced expression of stanniocalcin in tumor vasculature.

The references provided by Appellants confirm the correlation of expression of stanniocalcin and angiogenesis described in Appellants' specification. In addition, the references further confirm the association of expression of stanniocalcin and tumor tissue as described in Appellants' specification. The specification shows that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma

vasculature, but is not expressed in normal vessels. *See* the specification, for example, at page 145, line 32 to page 146, line 7 and Figures 28 and 29. Several of the post filing date references in the least confirm the correlation of expression of stanniocalcin in ductal mammary carcinoma and demonstrate similar results in other types of tumors. Therefore, one skilled in the art reading the specification would have a reasonable expectation that neutralizing or inhibiting antibodies to stanniocalcin would inhibit angiogenesis.

Appellants assert the evidence in the specification, as well as confirmatory evidence in the art shows that the specification enables the full scope of the claimed subject matter. Even if, in the unlikely event, that the Examiner is found to have met the initial burden for establishing that the claims are non enabled, Appellants submit they have provided evidence from others in the field that confirm the enablement of Appellants' claims. A number of different angiogenic models and different actual tumor tissue samples all consistently show a correlation between angiogenesis and the upregulation of expression of stanniocalcin in endothelial cells and tumor cells undergoing angiogenesis. One skilled in the art would expect based on Appellants' guidance and teachings in the specification and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists that treatment of a tumor with an agent that inhibits or neutralizes stanniocalcin inhibits angiogenesis. For at least these reasons, Appellants request reversal of the rejection of all of the claims.

EVIDENCE APPENDIX

A. OFFICE ACTIONS AND AMENDMENTS/RESPONSE

1. Examiner's Answer mailed November 20, 2008
2. Appeal Brief filed August 19, 2008
3. Notice of Appeal filed May 20, 2008
4. Interview Summary mailed February 20, 2008
5. Final Office Action mailed February 20, 2008
6. Amendment filed November 27, 2008
7. Non-Final Office Action mailed June 28, 2007
8. RCE, Amendment and Response filed April 11, 2007
9. Advisory Action mailed March 1, 2007
10. Notice of Appeal, Amendment After Final filed February 13, 2007
11. Final Office Action mailed October 13, 2006
12. Amendment filed July 25, 2006
13. Non-Final Office Action mailed April 25, 2006
14. RCE, Amendment under 37 C.F.R. § 1.1116 filed February 1, 2006
15. Notice of Appeal filed November 8, 2005
16. Final Office Action mailed August 10, 2005
17. Amendment and Response filed May 24, 2005
18. Non-Final Office Action mailed November 24, 2004
19. RCE, Amendment and Response filed September 2, 2004
20. Non-Final Office Action mailed March 5, 2004

21. Petition Decision granted February 11, 2004

22. Petition for Revival, Response to Notice of Non-Responsive Election filed August 6, 2003

23. Notice of Abandonment mailed July 30, 2003

24. Notice of Non-Responsive Election mailed January 9, 2003

25. Restriction Response filed October 29, 2002

26. Amendment filed August 14, 2002

27. Restriction Requirement mailed August 5, 2002

28. Sequence Listing filed May 29, 2002

29. Notice to Comply mailed April 22, 2002

30. Sequence Listed filed February 22, 2002

31. Notice to Comply with Requirements Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed January 23, 2002

32. Response to Notice to File Missing Parts August 24, 2001

33. Notice to File Missing Parts mailed February 22, 2001

34. Application filed October 31, 2000

B. REFERENCES RELIED UPON BY THE EXAMINER

1. U.S. Publication No. 2002/0042372 A1

2. U.S. Patent No. 5,773,876

3. Mook *et al.*, Biochim Biophys Acta, Vol. 1705:69-89, 2004, abstract

4. Dillman R.O., Annals of Internal Medicine, 111:592-603, 1989

5. Weiner L.N. Seminars in Oncology, 26 (4 Suppl 12): 41-50, August 1999

6. MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000

7. Jain, Scientific American, July 1994

8. Gura, Science, v278, 1997, pp. 1041-1042

9. Alberts *et al.*, Molecular biology of the Cell, 3rd edition, 1994, page 465

10. Lewin, B., Genes VI, Oxford University Press, Inc. NY, Chapter 29, 1997

C. REFERENCES CITED BY APPELLANTS

1. Olsen *et al.*, *Human Stanniocalcin: a Possible Hormonal Regulator of Mineral Metabolism* 93 Proc. Nat'l Acad. Sci. USA 1792 (1996).

2. Davis *et al.*, *An α2β1 Integrin-Dependent Pinocytic Mechanism Involving Intracellular Vacuole Formation & Coalescence Regulates Capillary Lumen and Tube Formation in Three-Dimensional Collagen Matrix* 224 Experimental Cell Res.39 (1996).

3. Filvaroff *et al.*, *Stanniocalcin 1 Alters Muscle & Bone Structure & Function in Transgenic Mice* 143 *Endocrinology* 3681 (2002).

4. McCudden *et al.*, *Co-localization of Stanniocalcin-1 Ligand & Receptor in Human Breast Carcinomas* 213 Molecular Cellular Endocrinology 167 (2004).

5. Wascher *et al.*, *Stanniocalcin-1: A Novel Molecular Blood & Bone Marrow Marker for Human Breast Cancer* 9 Clinical Cancer Res. 1427 (2003).

6. Yeung *et al.*, *Hypoxia-Inducible Factor-1 in Human Activation of Stanniocalcin-1 in Human Cancer Cells* 146 Endocrinology 4951 (2005).

7. Kahn *et al.*, *Gene Expression Profiling in an* In Vitro *Model of Angiogenesis* 156 The Am. J. of Pathology 1887 (2000).

8. Gerritsen *et al.*, *In Silico Data Filtering to Identify New Angiogenesis Targets From a Large* In Vitro *Profiling Data Set* 10 Physiological Genomics 13 (2002).

9. Folkman, *Angiogenic Inhibitors: A Fourth Modality of Anticancer Therapy* 4 Community Oncology 296 (2007).

10. Eccles, *Monoclonal Antibodies Targeting Cancer: 'Magic Bullets' or Just the Trigger?* 3 *Breast Can. Res.*, 86 (2000).

11. Presta *et al.*, *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors & Other Disorders* 57 Cancer Res. 4593 (1997).

13. Mook *et al.*, *The Role of Geltinases in Colorectal Cancer Progression & Mestasis* 1705 Biochemica Et Biophysica Acta 69 (2004).

14. Zlot *et al.*, *Stanniocalcin 1 is an Autocrine Modulator of Endothelial Angiogenic Responses to Hepatocyte Growth Factor* 278 Journal of Biological Chemistry 47654 (2003).

15. Press Release, Genentech, Inc. (Feb. 26, 2004).

D. CASES CITED IN THE BRIEF

1. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

2. *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976).

3. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

4. *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985).

5. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984).

6. *In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971).

7. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993).

8. *Falko-Gunter vs. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006).

9. *In re Cortright*, 165 F.3d 1353 (Fed. Cir. 1999).

10. *Ex parte Zhang*, Appeal 2008-2455 (Bd. Pat. App. & Int. 2008).

SUMMARY

It is earnestly requested that the Examiner's rejection be reversed for the reasons discussed herein, and that all of the pending claims be allowed.

Please charge any additional fees or credit overpayment to Merchant & Gould Deposit Account No. 13-2725.

Respectfully submitted,

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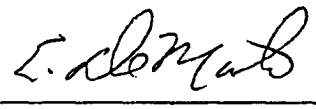
Date: January 21, 2009



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